Remarks

As amended, Applicants respectfully submit that claim 1 complies with the restriction requirement, i.e., by deleting the subscripts "n_2" and "n_3" from formula (I), and by deleting the phrase "n_2 and n_3 are each independently 0-3, provided that a sum of n_2 and n_3 is 0-4". Additional terms of claim 1 rendered redundant by the above amendments have also been deleted. These amendments are believed to be supported by numerous Examples in the specification. Applicants reserve the right to pursue the deleted subject matter in a subsequent Divisional Application.

Claim 18 has been amended by adding the phrase "a therapeutically effective amount of" as suggested by the Examiner.

No new matter is believed to have been added by the above amendments.

Non-elected claims 19 and 30-35 have been canceled without prejudice to their further prosecution in a subsequent Divisional Application.

Non-elected method claims 20-29 have been withdrawn by the Examiner. For the reasons stated below, Applicants respectfully submit that since the elected product claims are allowable for the reasons presented below, method claims 20-29 which depend from the allowable product claims should be rejoined (M.P.E.P. 821.04). Applicants respectfully request rejoinder of these claims.

Claims 1-18 and 20-29 are in the case. Claims 1-18 are presently active.

Rejection of Claim 18

The rejection of claim 18 under 35 U.S.C. §112, second paragraph is obviated by appropriate amendment. Applicants thank the Examiner for her suggestion, and have so amended claim 18. Applicants therefore request that the rejection be withdrawn.

Rejection over the Combination of **Baker** and **Patani**

The rejection of claims 1-10 and 18 under 35 U.S.C. §103(a) over the combination of Baker and Patani is respectfully traversed. The combination of Baker and Patani does not reasonably support a prima facie case of obviousness.

The basic requirements for a *prima facie* case of obviousness are:

1) the prior art references must teach or suggest all of the claim limitations (MPEP 2143.03).

2) there must be some motivation in the references themselves to modify the reference (MPEP 2143.01); and

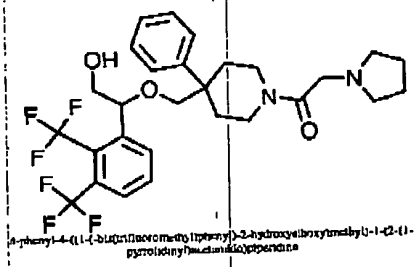
3) there must be a reasonable expectation of success. (M.P.E.P. § 2143.02)

*The Combination of **Baker** and **Patani** Does Not Teach or Suggest All Claim Limitations*

The compounds of the claimed invention are piperidines substituted at the piperidine ring nitrogen with a $-N(R^7)(N^{11})$ group. Thus, the piperidine compounds of the claimed invention must have an N-N bond at the piperidine ring nitrogen atom.

However, the generic description of Baker *excludes* compounds in which the piperidine ring nitrogen atom forms an N-N bond. Baker describes compounds in which a group "R^{3a}" is attached to the ring nitrogen atom. Group "R^{3a}" of the compounds of Baker can be any of 9 different generic substituents (i.e., H, COR^9, CO_2R^{10}, $COCONR^{10}R^{11}$, $COCO_2R^{10}$, SO_2R^{15}, $CONR^{10}SO_2R^{15}$, optionally substituted C_{1-6} alkyl, $Y\text{-}R^8$, or $CO\text{-}Z\text{-}(CH_2)_q\text{-}R^{12}$; at col. 3, lines 11-19). None of these groups "R^{3a}" of Baker form an N-N bond with the ring nitrogen atom. (Applicants note that the "$-NR^{10}R^{11}$" group at col. 3, line 14 of Baker is clearly one of the optional substituents of C_{1-6} alkyl, and therefore would not provide an N-N bond). Thus, Baker neither describes nor suggests a compound according to the claimed invention in which the ring N atom forms an N-N bond.

The Examiner points to Examples 8 and 17 of Baker as "analogous" to the compounds of the claimed invention. The structure of Example 8 is reproduced below (note that Example 17 is the "+" isomer of Example 8):

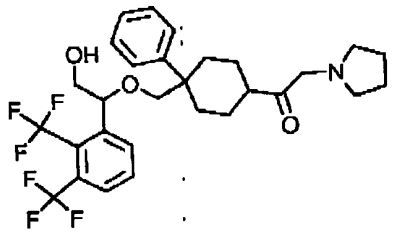


4-phenyl-4-[1-(-butyrolactonemethyl)phenyl]-3-hydroxyethoxymethyl-1-(2-(1-pyrrolidinyl)acetamido)piperidine

(Applicants note that the above structure is consistent with the experimental method for preparing Example 8 at col. 22 of Baker, in which the carboxylic acid group of (1-pyrrolidinyl)acetic acid, "activated" with i-butyl chloroformate and triethylamine, forms an amide bond with the piperidine ring nitrogen of the compound of Example 1.) As shown above, Examples 8 and 17 of Baker lack an N-N bond at the piperidinyl nitrogen atom.

The Examiner cites col. 5, line 57 of Baker, in support of her arguments. However, Applicants respectfully submit that the Examiner has misinterpreted Baker. Applicants note that the "pyrrolidinyl" described by Baker is an embodiment of R^{12} (not R^{11}). R^{12} is a substituent of the group "CO-Z-$(CH_2)_q$-R^{12}" of R^3. Compounds of Baker in which R^3 is CO-Z-$(CH_2)_q$-R^{12} would necessarily have a carbonyl group bonded to the ring nitrogen atom, and thus would not form an N-N bond at the ring nitrogen atom, as in the claimed compounds. Accordingly, the compounds of Baker having R^{12} = pyrrolidinyl must be quite different from the claimed compounds.

The Examiner appears to argue that Patani teaches that the –CO-CH_2- group linking the piperidinyl and pyrrolidinyl ring nitrogen atoms of Examples 8 and 17 of Baker may be replaced with amide, thereby providing a compound according to the claimed invention (i.e., since Patani indicates that *amide* and ketomethylene are considered bioisosteres). However, the –CO-CH_2- group of the compound of Baker shown above is *not* a ketomethylene group, because the carbonyl of the –CO-CH_2- group is bonded to the piperidinyl ring nitrogen. That is, the –CO-CH_2- group of Baker forms an amide group with the piperidinyl ring. Thus, following the teaching of Patani, replacing the amide group of Example 8 with a ketomethylene would form the following compound:



in which the amide nitrogen (i.e., the piperidinyl ring nitrogen) is replaced with "CH". Other bioisosteric replacements of amide taught by Patani in Table 48 would likewise provide compounds which also differ substantially from the claimed compounds.

Thus, the combination of Baker and Patani not only fails to teach or suggest all of the claim limitations of the claimed invention (i.e., the N-N bond of the claimed compounds), it also teaches away from the compounds of the claimed invention.

*There is No Reasonable Motivation in **Baker** and **Patani** to Modify the Compounds of Baker in the Manner Proposed by the Examiner*

Applicants note that Patani describes many different bioisosteric modifications, for example substitution of hydrogen with fluorine (p. 3149, col. 1), substitution of hydroxyl with amino (p. 3150, col. 1), substitution of hydroxyl with thiol (p. 3151, col. 1), substitution of hydrogen with hydroxyl, amino, and methyl (p. 3152, col. 1), interchange of chloro, bromo, thiol, and hydroxyl groups (p. 3154, col. 2), replacement of C=O with C=S (p. 3155, col. 2), interchange of –O-, -S-, $-CH_2-$, and -NH- (p. 3155, col.2 to p. 3156, col. 1), replacement of –CH= with –N= (p. 3156, col. 2), replacement of tertiary carbon with quaternary nitrogen (p. 3157, col. 1), replacement of phenyl with pyridyl (p. 3158, col. 1), replacement of cyclic with noncyclic structures (p. 3160, col. 2), etc. Thus, Patani teaches many different bioisosteric substitutions other than the specific substitution suggested by the Examiner. Indeed, Patani would as readily suggest modifications which do not provide compounds of the claimed invention (e.g., replacing the phenyl ring of Example 8 with pyridinyl, replacing the trifluoromethyl groups with methyl, replacing the ether linkage with –S- or $-CH_2-$, etc. In other words, Patani does not provide any particular direction as to which specific modification or combination of modifications would be most effective. Accordingly, there is no reasonable motivation found in Patani to modify the compounds of Baker in the manner proposed by the Examiner.

Furthermore, even if *arguendo* one were motivated to modify the piperidinyl amide of Example 8 of Baker, Table 48 of Patani provides *11 different* possible substitutions (exclusive of amide). However, Patani does not provide direction as to which bioisosteric substitution from Table 48 should be made. Moreover, none of the substitutions of Table 48 would provide a compound of the claimed invention (because all would lack an N-N bond).

Accordingly, Baker and Patani lack a reasonable motivation to provide the proposed modification.

*The Combination of **Baker** and **Patani** Does Not Provide a Reasonable Expectation of Success*

At page 3170, Patani states that "the ability of these groups [i.e., groups of Table 48] to be suitable bioisosteres depends on the role the amide group plays in eliciting the biological activity and the ability of the bioisostere to mimic this role as closely as possible." At page 3791, Patani describes various "ACAT" derivatives in which amide (group "X" of 98a) was replaced with various different bioisosteres (group "X" of 98b-98h), but only the "urea bioisostere 98e retained ACAT inhibitory activity". In other words, Patani teaches that successfully providing biologically active compounds by bioisosteric replacement is highly uncertain (note that only 1 of 8 different bioisosteres "retained ACAT inhibitory action *in vitro*"; Patani at p. 3171, col. 1), and success depends strongly on the particular biological mechanism by which the molecule acts (i.e., requiring an undue level of experimentation).

Accordingly, the combination of Baker and Patani not only fails to provide a reasonable expectation of success, but Patani affirmatively teaches that the probability of success is low.

For the reasons stated above, Applicants respectfully request that the rejection be withdrawn.

Rejection over the Combination of **Baker, Harrison, or CA 122:81123 and Patani**

The rejection of claims 1-10 and 18 under 35 U.S.C. §103(a) over the combination of Baker, Harrison, or CA 122:81123 ("CA") and Patani is respectfully traversed. The combination of Baker, Harrison, or CA 122:81123 ("CA") and Patani does not reasonably support a *prima facie* case of obviousness.

As discussed above, the compounds of the claimed invention have an N-N bond at the piperidinyl ring nitrogen, whereas all of the compounds of Baker lack an N-N bond at the ring nitrogen atom. Thus, the claimed compounds differ substantially from those of Baker.

The compounds of Harrison, like those of Baker, also lack an N-N bond at the ring nitrogen atom. See, for example the definition of R^3 at col. 2, lines 36-45 of Harrison, in which R^3 may be "H, COR^9, CO_2R^{10}, $COCONR^{10}R^{11}$, $COCO_2R^{10}$, SO_2R^{15}, $CONR^{10}SO_2R^{15}$", optionally substituted C_{1-6} alkyl, Y-R^8 (where Y is a

hydrocarbon chain of 1-4 carbon atoms), and CO-Z-$(CH_2)_q$-R^{12}. Thus, Harrison, like Baker, neither describes nor suggests a compound according to the claimed invention in which the ring N atom forms an N-N bond.

CA (which Applicants note is an abstract of the patent family which includes U.S. 5,620,989 – i.e., Harrison), like Baker and Harrison also fails to describe any compounds having an N-N bond at the ring nitrogen atom, as in the claimed compounds. Thus, CA, like Baker and Harrison, neither describes nor suggests a compound according to the claimed invention in which the ring N atom forms an N-N bond.

As discussed in detail above, Patani fails to provide an adequate motivation to modify the compounds of Baker, Harrison, or CA in the manner proposed by the Examiner. The Examiner proposes a quite specific modification to provide the claimed compounds, e.g., modifying the –C(O)-CH_2- group linking the piperidinyl and pyrrolidinyl rings of Example 8 of Baker. However, Patani describes many different possible bioisosteric substitutions, but does not provide any specific directions which would reasonably lead one of skill in the art to pick the specific modification proposed by the Examiner. Thus, for example, Patani as readily teaches replacing the phenyl ring of Example 8 of Baker with pyridinyl, as it does modifying the –C(O)-CH_2- group. Accordingly, none of the applied references provides a motivation for the proposed modification.

In addition, Applicants are unable to identify any bioisosteric substitution taught by Patani which would provide an N-N bond. Accordingly, the combination of the applied references fails to teach or suggest all of the claim limitations.

Moreover, Patani expressly teaches that bioisosteric replacement is highly uncertain, and success depends strongly on the particular biological mechanism by which the molecule acts (i.e., requiring an undue level of experimentation). Accordingly, there is no reasonable expectation that the proposed substitution would provide an effective compound. Indeed, the express teaching of Patani suggests otherwise.

Thus, the combination of the applied references fails to support a *prima facie* case of obviousness. Applicants therefore respectfully request that the rejection be withdrawn.

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Rejection over **Paliwal**

The rejection of claims 1-18 under 35 U.S.C. §103(a) over Paliwal is respectfully traversed. The Examiner has failed to support a *prima facie* case of obviousness.

The Examiner proposes that the compounds of Paliwal render the claimed compounds obvious because the compounds are "positional isomers" of the claimed compounds. However, "[h]omology should not be automatically equated with *prima facie* obviousness" (MPEP 2144.09). Furthermore, the case cited by the Examiner, *In re Dillon* (919 F.2d 688; 1990 U.S. App. LEXIS 19768; 16 USPQ.2d 1897), states:

> "This court, in reconsidering this case *in banc*, reaffirms that structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness" (emphasis added)

In other words, homology alone does not support a *prima facie* case of obviousness. The Office must also show how the prior art (i.e., Paliwal) suggests modifications which would provide the claimed compositions. Even if the Examiner is correct that the compounds of Paliwal and those of the present invention differ only in the positions of the substituents on the piperidine ring, Applicants fail to see where Paliwal suggests placing substituents at the specific positions so as to provide the claimed compounds. Indeed, Paliwal fails to provide any examples of 1,4,4-trisubstituted piperidines. Moreover, Paliwal also fails to describe piperidines having an N-N bond at the piperidinyl ring nitrogen atom. Accordingly, by the standards enunciated in *In re Dillon*, Paliwal does not reasonably suggest the claimed compounds.

Furthermore, it is virtually axiomatic in the pharmaceutical arts that even small differences in structure can impart substantial differences in biological activity – i.e., the differences in biological activity of stereoisomers of amino acids, etc. Thus, without the benefit of improper hindsight, one of ordinary skill in the pharmaceutical arts would not have a reasonable expectation that modifying the compounds of Paliwal in the manner proposed would provide useful compounds.

Accordingly, for the reasons stated above, Applicants respectfully submit that the Examiner has failed to support a *prima facie* case of obviousness. Applicants therefore request that the rejection be withdrawn.

Provisional Obviousness-Type Double Patenting Rejection Over **Paliwal**

The provisional rejection of claims 1-18 under the judicially created doctrine of obviousness-type double patenting is respectfully traversed. The discussion above also applies to the subject matter claimed in Paliwal:

1. Paliwal fails to provide any motivation for modifying the structures of the compounds claimed therein, to provide compounds according to the claimed invention.
2. Modifying the claimed compounds of Paliwal in the manner suggested would not reasonably be expected to provide useful compounds (i.e., that is, without improper hindsight).

Accordingly, the subject matter claimed in Paliwal does not reasonably suggest the claimed invention. Applicants therefore respectfully request that the rejection be withdrawn.

Applicants also note that a provisional rejection of the claims under the judicially created doctrine of obviousness-type double patenting should also be withdrawn when it is the only remaining rejection in the case (MPEP 804 (I)(B)).

Respectfully submitted,
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